

Demographic and Pathologic Factors Contributing to a Growth Rate Model of p16-Negative Oral Cavity Squamous Cell Carcinoma

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Introduction

Squamous cell carcinoma represents a unique clinical entity in head and neck oncology, accounting for approximately 95% of malignancies arising throughout the oropharyngeal tract.¹ Specifically, oral cavity squamous cell carcinoma (OSCC) arises from the mucosal lining of the lip, anterior tongue, floor of mouth, buccal mucosa, retromolar trigone, or hard palate. Complex anatomical interfaces in the oral cavity may result in OSCC exhibiting unpredictable growth patterns between initial clinical assessment and surgical excision, requiring more radical intervention than anticipated.² Consequently, a thorough understanding of demographic and pathologic factors associated with OSCC growth patterns will yield important clinical insight.³

In head and neck cancer, delays between diagnosis and surgical treatment lead to disease progression, poorer outcomes, and increased risk of death.^{3, 4} Dutch population-based data has shown treatment delays of thirty days past baseline result in 20% death hazard increases, and are associated with low socioeconomic status, male sex, and referral from a peripheral center.⁴ Comparably, Southwestern Ontario data specific to OSCC has shown decreases in operating room access of 10% increase disease recurrence by 59%.³ Additionally, individuals seen by a head and neck surgeon for primary malignancy workup preceding a month with below-average operating room hours were found to have a higher risk of disease recurrence and death.³

When examining tumours of the oral cavity, intricate anatomy invites complexity to the analysis of cancers easily measured on superficial dermatologic structures or high-resolution abdominal CT; dental amalgam may cause artifact and distortion, limiting the clinical utility of cross-sectional imaging. Limited previous work has examined the role of growth rate in anatomically-complex OSCC. Diffusion-Weighted MRI models have shown strong predictive value for assessing tumour growth rate in head and neck SCC patients; however, no extractable data specific to the oral cavity was presented.⁵

In the current study, we employ a cursory model of oral cavity growth for the purpose of examining oral cavity tumour growth rate. We aim to quantify the growth rate of p16-negative oral cavity squamous cell carcinoma, characterize causative relationships between demographic risk factors and tumour growth, and examine pathologic findings associated with tumour growth rate at a tertiary care institution.

Methods

Participants were prospectively recruited from the referral list of the Multidisciplinary Head and Neck Cancer Clinic at London Health Sciences Centre (LHSC), London, Ontario, Canada. Eligibility was determined based on a biopsy-proven diagnosis of squamous cell carcinoma. Human papillomavirus strain 16-positive tumors, as determined on initial biopsy pathology, were excluded. Participants were considered for inclusion if scheduled for surgical resection with curative intent, with no chemotherapeutic or radiotherapeutic treatment over the pre-operative interval. Participation in this study had no bearing on clinical treatment decisions. Eligible participants were explained details of the study, questions were answered to their satisfaction, and written consent was obtained. Demographic information was collected from consented participants via consultation record and supplemented with telephone interview, including age, sex, smoking history, alcohol consumption history, previous all-type malignancy, previous chemotherapy treatment, and previous head or neck radiation exposure.

Initial antero-posterior (A-P), craniocaudal (C-C), and depth of invasion (DOI) tumour measurements were collected by a trained head and neck radiologist from the first captured head and neck computed tomography (CT) scan identifying the presenting malignancy. Upon surgical resection, tissues were oriented to the anterior and caudal directions, fixed in 10% formalin solution, and processed per standard LHSC pathological sample protocol. After 24 hours of tissue fixation, equivalent A-P, C-C, and DOI dimensions of the specific tumour were collected by the attending pathologist. Values were corrected by a literature-based coefficient of spatial shrinkage, to account for resection- and formalin-caused tissue deformation.⁷

Tumour volume was approximated at the date of initial imaging and the date of resection as one-half the product of maximum dimensions in the A-P, C-C, and DOI orientations. The cumulative pre-operative interval was defined at the elapsed time between initial CT scan and date of resection, recorded in days. Linear growth rate was determined over the pre-operative interval in cm³/week.

Pathologic information was collected from resected tumour, including pathological ‘T’ stage, pathological ‘N’ stage, grade, site of origin, focality, presence of lymphovascular or perineural invasion, number of nodes examined operatively, and minimum attained surgical margin. Regression analysis was used to assess causal relationships between demographic and pathologic factors—as collected from patient interview and pathologic analysis—and squamous cell carcinoma tumour growth. Preliminary analyses were performed to ensure no violation of assumptions of normality, linearity, and multicollinearity. Multifactorial regression was applied to assess the influence of independent demographic factors of age, sex, smoking history, alcohol consumption history, previous all-type malignancy, previous chemotherapy treatment, and previous head or neck radiation exposure on variability of tumour growth rate. Unilinear regression was used to assess the impact of tumour growth rate on pathological ‘T’ stage, pathological ‘N’ stage, grade, site of origin, focality, presence of lymphovascular or perineural invasion, number of nodes examined operatively, and minimum attained surgical margin.

Results

Factor	Coefficient	R ²	p Value	95% CI	
				Lower	Upper
Tumour Stage	0.001	0.182	0.112	1.84	3.30
Nodal Stage*	0.002	0.291	0.038	-0.48	0.74
Subsite	Lateral Tongue	0.000	0.053	0.411	0.03
	Buccal Mucosa	0.001	0.248	0.059	-0.05
	Oral Floor	0.000	0.025	0.576	-0.07
	Central Tongue	0.000	0.012	0.699	-0.09
	Retromolar Trigone*	0.001	0.351	0.020	-0.18

Table 1. Pathologic correlates to tumour growth rate. * denotes significant associations.

Factor	Coefficient	R ²	p Value	95% CI	
				Lower	Upper
Age	5.715	0.693	0.235	-4.68	16.11
Sex	-158		0.460	638.54	321.13
Smoking	-5.675		0.629	-14.85	3.50
Alcohol Use*	85.720		0.014	23.51	147.94
Previous Cancer	-146.196		0.662	-904.42	612.03
Previous Chemotherapy	-82.723		0.852	-1095.25	929.81
Previous Radiotherapy	-161.610		0.686	-1066.72	743.50

Table 2. Clinical correlates to tumour growth rate. * denotes significant associations.

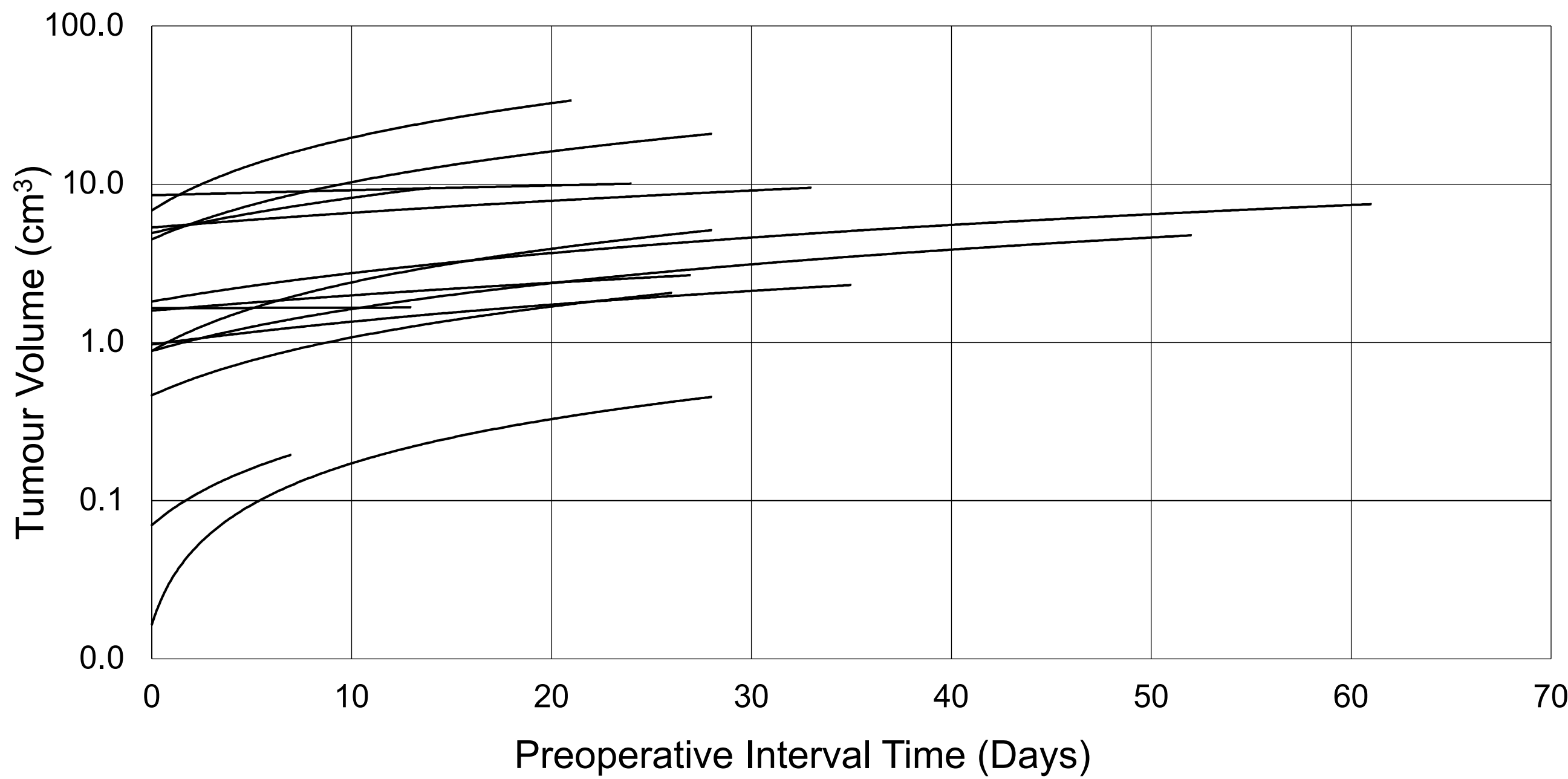


Figure 2. Logarithmically-modelled individual tumour growth of participating patients.

Discussion and Conclusions

Alcohol use has long been acknowledged as a primary risk factor for OSCC pathogenesis.² While no specific mechanism is viewed as solely responsible, the most widely accepted explanation is a combination of systemic immunosuppression, checkpoint inhibitor downregulation, and DNA hypomethylation altering oncogene expression and allowing uncontrolled cell division.⁹ Previous systematic reviews have shown the relative risk OSCC development in heavy alcohol drinkers to be 5.13, as compared to light or non-alcohol drinkers.¹⁰ However, these patients are also at an increased risk of carcinoma development in the oropharynx and hypopharynx, due to prolonged carcinogenic exposure time. Future work in this field will continue to examine potential mechanism for this relationship, and its interplay with increase pathogenic risk of OSCC development. Previous multivariate analysis has shown that masticator space involvement, neck recurrence, and cervical metastasis were all negative predictive factors for prognosis.¹¹ Previous retrospective cohort data has shown the efficacy of isolated radiation on treating early stage RMT carcinoma, as surgical treatment modalities often require extensive resections and reconstructions.¹² Finally, a causative relationship was found to exist between tumour growth rate and nodal stage, per standard TNM staging schematic. In OSCC, this translates to an increased rate of cervical lymph node metastasis.¹³ Previously, high tumour thickness has been linked to higher rates of nodal metastasis, and ‘N’ stage.¹⁴ Though this has not been examined in the current paper, rapid tumour growth is likely associated with a high Ki-67 index and VEGF-A expression: indicators of increased cell turnover and worsened morbidity.¹⁵ Presence of Ki-67 and VEGF-A have been implicated in nodal metastasis in head and neck cancer, as well as increase mortality.¹⁵

Multifactorial and unilinear regression analysis were used to determine causative relationships between pathological and clinical correlates, which examine the responsibility for variance within a dataset. Additionally, data collection was performed using a combination of radiologic and pathologic techniques, resulting in potential error at the comparison process. As we are assessing relative growth, this may impact reported growth rate; however, relationships with causative variables are unlikely to be impacted.

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